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United States Patent and Trademark Office Attn: Examiner Alana M. Harris Art Unit: 1642	(571) 272-0831	(703) 872-9306

From : Barry S. Wilson
Date : May 7, 2004
Client/Matter No : 039316-0301
User ID No : 3067

MESSAGE:

Re: U.S. Patent Application No. 09/438,917
Our Ref.: 039316-0301 (Formerly P-IU-3446

Dear Examiner Harris,

Attached please find a copy of the Office Action dated 06/17/2003. The Office Action includes the initialed pages from the 1449 that were missing from your file. If you have any questions you can contact me or my secretary, Germaine Sarda, at (858) 847-6759.

Sincerely,

Barry S. Wilson

If there are any problems with this transmission or if you have not received all of the pages, please call .

Operator:	Time Sent:	Return Original To: Germaine Sarda

PAGE 1/16 * RCVD AT 5/7/2004 12:18:01 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/4 * DNIS:8729306 * CSID: * DURATION (mm-ss):05-14

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/438,917	11/12/1999	PETER J WELCH	P-IU-3446	1019

7590 06/17/2003

Barry S. Wilson
FOLEY & LARDNER
402 West Broadway 23rd Floor
San Diego
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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Date: 6-24-03
FROM: DOCKETING DEPARTMENT
Due 9-17-03; DD-12-17-03
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039316-0301
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PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/438,917	WELCH ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3, 4 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *24* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Claims 3, 4 and 11 are pending.

Claims 1, 2 and 5-10 have been cancelled.

Claim 11 has been added.

Claims 3, 4 and 11 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. Applicants were notified in the first action on the merits, Paper number 20 that the information disclosure statement (IDS), Paper number 9 filed February 14, 2000 failed to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it improperly cited references on pages 2-4, which did not include dates of publication and were not provided. The newly submitted IDS (received March 6, 2003) contains the proper information for references from Paper number 9 and these references have been reviewed by the Examiner.

Maintained Objection

Drawings

4. Two new drawings, Figures 2A-2D and 5A-5F were submitted February 26, 1003 as Paper number 22. The Draftsman deemed these particular drawings acceptable. However, other drawings continue to be objected to because of reasons cited on attached form, PTO948 completed by the draftsman attached with the instant action. Correction is required.

Withdrawn Objection

Specification

5. The disclosure is no longer objected to because it no longer contains an embedded hyperlink and/or other form of browser-executable code.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

6. The rejection of claims 3 and 4 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn. Claims 1 and 2 have been cancelled.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

7. Claims 3, 4 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In light of the specification the claimed nucleic acid sequence has greater than 95% sequence identity over the entire length of the nucleic acid sequence shown as SEQ ID NO: 5, see page 9, lines 14-27.

Applicants argue that Examples II, IV and V within the specification demonstrate tumor suppressor activity of the claimed tumor suppressor nucleic acid and that such assays are used for diagnostic analysis of tumor suppressor activity. Furthermore, Applicants aver that the claims are directed to a nucleic acid composition and no a method human therapy and as such Applicant need only enable use of the composition in cultured cells. These points of view have been considered and found unpersuasive.

a. Applicants broadly claim a substantially pure nucleic acid molecule comprising a nucleic acid sequence that has greater than 95% sequence identity with the nucleic acid sequence shown as SEQ ID NO: 5. The native tumor suppressor nucleic acid sequence designated Human Suppressor-1 (HTS1) is depicted as SEQ ID NO: 5 consisting of 1664 nucleic acids. However, the claims also encompass undefined nucleic acid sequences in which 5% of the sequences have been changed, hence have

not been described. Moreover, this divergent protein may not embody the tumor suppressor activity as native protein, SEQ ID NO: 6. While one of skill in the art can theoretically produce all of these nucleic acid sequences and proteins with art known techniques such as site-directed mutagenesis it would still be burdensome to one of skill in the art to produce all of these different combinations and thereafter determine their activity. Likewise, it is not clear what criteria would be used in deciding which nucleic acids and amino acids and how many of them would and could be substituted from the remaining 1664 and 473 sequences, respectively resulting in an effective tumor suppressor molecule. It is art known that certain residues are shown to particularly important to the biological or structural properties of a protein or peptide, e.g., residues in active sites and such residues may not be generally be exchanged. The true fact of the state of the art in peptide chemistry is expressed succinctly in the accompanying Lazar article (Molecular and Cellular Biology 8(3): 1247-1252, March 1988). This article presents data that substantiates the fact that the introduction of mutations in an amino acid sequence will yield products with different biological activity from the wild type protein.

There is no guidance of record setting forth the strategy of obtaining the broadly claimed nucleic acids which may not encode a tumor suppressor protein which is to be useful in the applications set forth in the specification, see pages 36, line 12-page 38, line 21; page 41, line 1-page 42, line 14 and page 43, lines 3-26. The peptide art is unpredictable with regard to determine what peptides resulting form deletions, additions, mutations or analogues would be biologically active. Since the amino acid sequence of

a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acid or acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. The specification provides essentially no guidance as to which of the infinite possible choices is likely to be successful, especially in view of the non-conservative nature of some of the changes that can be made according to the disclosure in the specification. Without such guidance, the changes which must be made in the sequences of the wild-type/native HTS1 nucleic acid, which results in a protein other than SEQ ID NO: 6 and retaining tumor suppressor function is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

b. Applicants remind the Examiner that they need only enable use of the composition in cultured cells, however the claims are given the broadest interpretation which does not preclude its intended use of being administered to an individual as suggested in the specification, see page 36, line 12-page 38, line 21. Applicants note the uses of the claimed molecule, however there is no nexus between their use in *in vitro* cultured cell assays and the noted uses of a diagnostic tool and as an *in vivo* therapeutic. The specification fails to establish a correlation between the *in vitro* assays establishing tumorigenic state and effectiveness of the candidate tumor suppressor *in vivo*. The specification provides insufficient guidance as to which types of

tumor cells the tumor state can be suppressed or the manner at which suppression is accomplished. Assuming that HTS1 is a tumor suppressor protein, it is not immediately obvious that the administration of that the HTS1 polynucleotide and polypeptides encoding HTS1 would be effective to treat or prevent cancer. For instance, in the case of p53, which is an established tumor suppressor gene, a review was recently published by Malkin (Journal of Neurooncology 51(3):231-243, February 2001) discussing how best to harness the p53 to induce cellular growth arrest and cell death and generate novel effective approaches to cancer therapy. Clearly, after two decades of studying the properties of p53, methods of inhibiting tumor progression and initiation by means of p53 are not yet in hand. Thus, there is no nexus between the *in vitro* effectiveness of a candidate tumor suppressor molecule and it's *in vivo* status, i.e. ability to treat or prevent cancer. One skilled in the art could not be expected to correlate the results of an *in vitro* assay with any outcome of an *in vivo* assay.

The specification fails to provide sufficient guidance to enable one of skill in the art to make and use the claimed nucleic acid molecules and their corresponding polypeptides in a manner reasonably correlated with the broad scope of the claims. Accordingly, SEQ ID NO: 5, 6 and molecules sharing 95% sequence identity are not enabled and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
June 10, 2003

PTO/SB/08 (08-00)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: September 10, 2002

(Use as many sheets as necessary)

1 of 2

Complete if Known	
Application Number	09/438,917
Filing Date	11/12/1999
First Named Inventor	Welch, et al.
Group Art Unit	1642
Examiner Name	Alana M. Harris
Attorney Docket Number	039316-0301

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Document Number	U.S. Patent Document Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Office[3]	Number[4]	Kind Code[5] (if known)	Name of Patentee or Applicant of Cited Documents	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
AMH	A1		WO/00 05415		Barber, Jack			
AMH	A2		WO/00 15799		Tang, Y. Tom			
AMH	A3		WO/98 32880		Barber, Jack			
	A4		WO/99 02675		Communi Didier			
✓	A5		WO/99 53031		Teymuras, Kurzchalia			

Examiner Signature	AMHarris	Date Considered	5/21/2003

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Date Submitted: September 10, 2002

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Sheet 2 of 2

Complete if Known	
Application Number	09/436,917
Filing Date	11/12/1999
First Named Inventor	Welch, et al.
Group Art Unit	1642
Examiner Name	Alana M. Harris
Attorney Docket Number	039316-0301

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
AMH	A6	Ahn, et al., "Identification of cDNAs for Sox-4, an HMG-box protein, and a novel human homolog of yeast splicing factor SSF-1 differentially regulated during apoptosis induced by prostaglandin A2/delta12-PGJ2 in Hep3B cells," *Biochemical and Biophysical Research Communications*, 260:216-221 (1999)	
	A7	Nylandsted, et al., "Expression of a p16INK4a-specific ribozyme downmodulates p16INK4a abundance and accelerates cell proliferation," *FEBS Letters*, 436(1):41-45 (1998)	
	A8	Suarez-Huerta, et al., "Cloning, genomic organization, and tissue distribution of human Ssf-1," *Biochemican and Biophysical Research Communications*, 275:37-42 (2000)	
	A9	Welch, et al., "Identification and validation of a gene involved in anchorage-independent cell growth control using a library of randomized hairpin ribozymes," *Genomics*, 66:274-283 (2000)	

Examiner Signature	AMHarris	Date Considered	9/27/2003

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: February 6, 2003

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Sheet 1 of 3

Complete if Known	
Application Number	09/4 917
Filing Date	11/12/99
First Named Inventor	Welch
Group Art Unit	1642
Examiner Name	A. Harris
Attorney Docket Number	P-IU 3446

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		GENBANK AA495929 (June 30, 1997)
		GENBANK AA583557 (September 5, 1997)
		GENBANK AI247609 (November 4, 1998)
		GENBANK AB016160 (January 22, 1999)
		GENBANK AF030453 (November 24, 1998)
		GENBANK AB016161 (January 22, 1999)
		GENBANK AC003104 (June 25, 1998)
		GENBANK AI078456 (August 10, 1998)
		GENBANK Z54280 (January 15, 1997)
		GENBANK AI084732 (August 17, 1998)
		GENBANK AC005739 (October 1, 1998)
		GENBANK AI147476 (September 29, 1998)
		GENBANK X68128 (June 1, 1994)
		GENBANK C73064 (September 22, 1997)
		GENBANK Z98755 (November 23, 1999)
		GENBANK D24303 (December 2, 1993)
		GENBANK R12420 (April 12, 1995)
		GENBANK D42474 (May 4, 1998)
		GENBANK AI359294 (January 6, 1999)
		GENBANK D46041 (March 9, 1995)
		GENBANK AC006022 (December 21, 1999)
		GENBANK H28699 (July 14, 1995)
		GENBANK AB014571 (February 6, 1999)
		GENBANK T92983 (March 22, 1995)
		GENBANK AA406194 (May 1, 1997)

Examiner Signature	Ann Harris	Date Considered	5/27/2003

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Date Submitted: February 6, 2003

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Sheet	3	of	3

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		GENBANK X64080 (December 15, 1997)	
		GENBANK X98523 (October 30, 1996)	
		GENBANK D26094 (Dec 3, 1993)	
		GENBANK AJ011930 (November 11, 1998)	
		GENBANK Y00057 (July 28, 1995)	
		GENBANK AC005668 (September 10, 1998)	
		GENBANK M15395 (January 6, 1995)	
		GENBANK U94776 (June 1, 1998)	
		GENBANK AA158729 (June 24, 1997)	
		GENBANK AA357439 (April 21, 1997)	
		GENBANK AA600873 (September 23, 1997)	
		GENBANK W87345 (June 24, 1996)	
		GENBANK AB000909 (April 7, 1998)	
		GENBANK AA492602 (June 25, 1997)	
		GENBANK AF067845 (February 8, 1999)	
		GENBANK AI325663 (December 23, 1998)	
		GENBANK AA575760 (September 21, 1997)	

Examiner Signature	AMHarris	Date Considered	5/27/2003

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		GENBANK W84786 (September 6, 1996)	
		GENBANK AA278399 (April 2, 1997)	
		GENBANK W84633 (September 6, 1996)	
		GENBANK AI147481 (September 29, 1998)	
		GENBANK AA211219 (January 16, 1997)	
		GENBANK L00634 (June 12, 1993)	
		GENBANK AA571392 (August 27, 1997)	
		GENBANK L10413 (January 30, 1996)	
		GENBANK AA160809 (June 24, 1997)	
		GENBANK D29973 (February 7, 1999)	
		GENBANK S69381 (September 23, 1994)	
		GENBANK AA511830 (July 8, 1997)	
		GENBANK Z82189 (December 12, 1999)	
		GENBANK AA474138 (June 18, 1997)	
		GENBANK AC005165 (June 20, 1998)	
		GENBANK C85533 (March 2, 1998)	
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		GENBANK AA408064 (May 2, 1997)	
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		GENBANK AI326830 (December 23, 1998)	
		GENBANK AA070605 (October 27, 1997)	
		GENBANK AA655540 (November 4, 1997)	
		GENBANK AC003957 (December 29, 1997)	
		GENBANK AC003695 (October 29, 1998)	
		GENBANK U09941 (March 14, 1995)	
		GENBANK AC002091 (May 13, 1997)	

Examiner Signature	Ann Harris	Date Considered	9/27/2003

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case. Any

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